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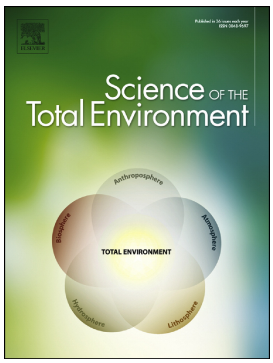

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COVID-19 effective reproduction number dropped during Spain's nationwide dropdown, then spiked at lower-incidence regions

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Short title: COVID-19 infection thresholds in Spain

Abstract

COVID-19 pandemic has rapidly spread worldwide. Spain has suffered one of the largest nationwide bursts, particularly in the highly populated areas of Madrid and Barcelona (two of the five largest conurbations in Europe). We used segmented regression analyses to identify shifts in the evolution of the effective reproduction number (Rt) reported for 16 Spanish administrative regions. We associate these breaking points with a timeline of key containment measures taken by national and regional governments, applying time lags for the time from contagion to case detection, with their associated errors. Results show an early decrease of Rt that preceded the nationwide lockdown; a generalized, sharp decrease in Rt associated with such lockdown; a low impact of the strengthened lockdown, with a flattening of Rt evolution in high-incidence regions, and even increases in Rt at low-incidence regions; and an increase in Rt associated to the relaxation of the lockdown measures in ten regions. These results evidence

the importance of generalized lockdown measures to contain COVID-19 spread, and the limited effect of the subsequent application of a stricter lockdown (restrictions to all non-essential economic activities). Most importantly, they highlight the importance of maintaining strong social distancing measures and strengthening public health control during lockdown de-escalation.

Keywords: COVID-19; Spain; Regional variation; Rt, Policy responses; Lockdown; De-escalation

Highlights:

- Public health and movement restriction measures can limit the spread of infectious diseases in highly-populated regions.
- We associate governmental containment measures with the dynamics of COVID-19 transmission in Spain.
- The national lockdown successfully decreased Rt in all regions, but the effectiveness of the strengthened lockdown varied considerably among regions.
- Increases in transmission are associated with higher mobility within and between regions.
- Enhanced contact tracing is needed to prevent disease transmission without the need to recourse to new lockdowns.

1. Introduction

The rapid spread of COVID-19 pandemic has led to over 25 million confirmed cases from 31 December 2019 to 30 August 2020 (Dong et al., 2020). Such growth has been spatially heterogeneous, with large differences between countries, and between regions within countries (e.g. Gatto et al., 2020). These differences were partly due to their different responses to the WHO alert, based on the resources and structure of their health and R&D systems, and the ability to implement social distance measures (Fernández-Recio, 2020; Dehning et al., 2020). But also to their international connectivity (Coelho et al., 2020), the specific strains reaching each territory (see updated data at nextstrain; Hadfield et al., 2018) and the age and spatial structure of their human populations (Gatto et al., 2020). Response within countries has also been heterogeneous, particularly for those with decentralized governance structures – such as the federal states of USA, Germany and Brazil, or the administrative regions of Italy or Spain (Cheng et al., 2020).

COVID-19 arrived to mainland Spain at least in early February (first recorded hospitalization dates back to 15 February; Table S1), if not before (see Deslandes et al., 2020). During February, COVID-19 infection reached Spain repeatedly, mainly via UK, Italy and China – as evidenced by the presence of fourteen different genetic clusters identified by nextstrain (Hadfield et al., 2018; data from 27 April 2020). The combination of these repeated introductions with early, unnoticed community transmission resulted in consecutive outbreaks in distant, highly populated areas of the Basque Country and Navarra (North), Madrid (Center), Catalonia (North East), Andalusia (South) and Valencia (East). It is reasonable to assume that, by early March, COVID-19 infections were widely distributed throughout the whole country. The pandemic peaked, however, most strongly in Madrid (around 6.4M people; second most populated metropolitan area of the EU, after Paris) – to the point that 65-67% of local

incidence and mortality at the 52 Spanish provinces is explained by their early-stage mobility from and to Madrid (Mazzoli et al., 2020).

The adoption of containment measures by the national and regional governments followed a sustained increment through time until the beginning of May, when the government started a phase of progressive relaxation and de-escalation (Table 1; see also Table S1). Alike Italy (Gatto et al., 2020) or Germany (Dehning et al., 2020), these governmental restrictions on mobility and personal contact had a positive impact on COVID-19 containment, albeit with significant regional differences (Pollán et al., 2020). Indeed, personal hygiene and social distancing recommendations coincided with an early deceleration in the spread of the disease, and the progressive enforcement of harder isolation lockdown measures (Table 1) did so with the containment of the disease outbreak by early April in both the whole of Spain, and the densely populated Madrid and Catalonia regions (Santamaría & Hortal, 2020). In this paper, we use official daily estimates of the effective reproduction number (Rt) at regional level to evaluate the responses of the pandemic to early containment measures (social distancing and hygiene, nationwide lockdown, and strengthened lockdown) and their subsequent relaxation.

Table 1. Main sequence of public health and movement restriction measures taken by national and regional governments (i.e. *Comunidades Autónomas*) in Spain during the first phase of the COVID-19 pandemic (until 20th May 2020). See Table S1 for more detailed information.

Starting time	Policy measures
Late February – early March	Recommendation of preventive measures
9-10 March	Increasingly stricter social-distancing measures
15 March	Nationwide lockdown (announced 13 March)
31 March	Strengthened lockdown (all non-essential activities banned)
13 April	Cessation of the strengthened lockdown
26 April	Relaxation of lockdown: outings by children allowed
4 May -	Relaxation of lockdown: outings for elderly and adults on sport/leisure activities allowed
11 May	Cessation of lockdown (advanced to 4 May in some Balearic and Canary Islands, delayed in Madrid, Catalonia, Castilla-León, Valencian Community and Castilla-La Mancha until as late as 21 May).

2.Data and methods

2.1. Infection and fatality data

Official data were obtained from the centralized panel on the situation and evolution on the COVID-19 pandemic in Spain (COVID-19 Panel: https://cnecovid.isciii.es/covid19/) run by the National Epidemology Center (Instituto de Salud Carlos III – CNE-ISCIII) and the Spanish Ministry of Health. Daily estimates of the basic reproduction number (Rt) aggregated at regional level (autonomous regions) were extracted from the panel site (https://cnecovid.isciii.es/covid19/#declaraci%C3%B3n-agregada). Data were retrieved for all Spanish Autonomous Communities (regions hereafter) except the Canary Islands, Ceuta and Melilla – which were excluded because of their small size and/or isolated geographic location.

Estimates are based on cumulative data (PCR-confirmed cases until the day of reporting) provided by the regional governments to the Ministry of Health National Epidemiological Surveillance Network RENAVE, using a seven-day aggregation window to account for uneven daily reporting. Dates for each case were assigned to the date of start of symptoms or, failing this, to the date of diagnosis minus 6 days, the median lag between first symptoms and case reporting from the onset of the disease in Spain until 10 May 2020 (following CNE-ISCIII, 2020). Effective reproduction numbers were calculated in R EpiEstim v. 2.2-1 package (Cori et al., 2019), assuming a Poisson distribution, and using a Bayesian framework to estimate credible serial intervals for infections (see Cori et al., 2013) with the parametric_si option in EpiEstim, where the mean and SD of the serial interval were also based on the analysis of the whole RENAVE dataset until May 10th (A. Larrauri and D. Gómez-Barroso, personal communication; see also https://cnecovid.isciii.es/covid19/#documentaci%C3%B3n-y-datos). RENAVE data series was discontinued on 10 May 2020, owing to changes in the reporting procedures associated to the new Vigilance and Control Strategy – which required a re-consolidation of existing data before the addition of new ones. However, data following the criteria from the original series was made available until late May, allowing to extend the series describing the onset of COVID-19 in Spain until late May.

The time series used for the analysis ranges from 14 March 2020 –the first date for which data were available for all regions, and 20 May 2020 –when data updating was temporarily halted (see above). Hence, it starts the day in which the nationwide lockdown was declared, and finishes nine days after the onset of the de-escalation. We used the official estimates of Rt, instead of our own calculations based on reported numbers of cumulative cases, because continued update of the latter (to correct for disparities in the reporting times and procedures of the different regional authorities) by the central authority, without reporting clearly on the procedures or changes made, makes the former more reliable. Given the uneven PCR testing during the onset of the pandemic, it could be argued that direct

epidemiological parameters such as deaths or hospitalizations could be more reliable as indicators of COVID-19 spread during the period analyzed. However, the unevenness of both contagion rates and severity of the disease along age classes in the Spanish population during this period (see CNE-ISCIII, 2020) may bias these parameters. In any case, an independent analysis of cumulative numbers of reported cases and deaths (Santamaría & Hortal, 2020) showed that the patterns found for both epidemiological parameters were largely consistent during the onset of the pandemic in the whole of Spain, and Madrid and Catalonia regions. Therefore, we are relatively confident that diagnoses from swabs have tracked the same dynamics as deaths, at least in the case of Spain and Spanish regions during the first months of COVID-19 spread.

2.2. Lag time estimates

The calculation of Rt values of reported cases was based on the date of symptom onset, as declared in each case report. When this information was not available, it was replaced by the date of testing, plus an estimate of the time from illness onset to testing (median = 6 days, based on 158,094 diagnosed cases; CNE-ISCIII, 2020). To assign estimated Rt values to the date of infection, we used infection-to-symptom onset times based reported values of incubation time - with mean and median values ranging from 5·0 to 6·4 days (Lauer et al., 2020; Linton et al., 2020; Lai et al., 2020), which we rounded to 6 days for simplicity.

2.3. Analyses

We used segmented (i.e. broken-line) regressions to identify breakpoints in the temporal behavior of effective reproduction number (Rt) values in the 16 Spanish regions analyzed. Changes in the slope of daily Rt values are taken to represent shifts in COVID-19 transmission

trends. We fitted a family of segmented regressions ranging from zero to eight breaking points, with a minimum of five data points per segment, and compared them using their respective BICs, using the breakpoints function in strucchange R package (Zeileis et al., 2002), with recourse to lme4 pacakage (Bates et al., 2020) for the calculation of the best-model's intercepts and slopes. All calculations were made in R 3.6.3 (R Core Team, 2020).

The algorithm of strucchange's breakpoints uses separate intercepts at each different segment, thus allowing for discontinuities in the fitted functions – i.e., for the separate identification of both progressive increases or decreases in Rt, and sudden "jumps" or "plunges" in daily values of this parameter. We chose to use a breakpoint procedure resulting in discrete regression segments, instead of a procedure using near-continuous ones (e.g. R's 'segmented' function), to allow for the identification of such sudden changes. While it is important to bear in mind that such changes could reflect uneven reporting, we also considered that: (i) Sudden jumps in Rt, linked to bouts of infection, are not unusual in the dynamics of the COVID-19, as indicated by the detection of local outbreaks involving tens (or even hundreds) of contagions during single-day events in June-August 2020, in virtually all regions. (ii) While some of these jumps could be related to systematic reporting errors, the use of Rt values based on a 7-day time-window sufficed to eliminate the main source of variability linked to reporting: the decrease in reporting during weekends, which caused cases to peak on Tuesdays-Thursdays and plunge on Friday-Sunday (as confirmed by the general lack of significant autocorrelations at lag>2 in our models, see below). (iii) To avoid sudden jumps caused by non-systematic reporting errors (which should be followed by a quick return to the previous, baseline values), we constrained the model to identify slope changes involving a minimum of 5 data-points. (iv) Detecting such changes using a near-continuous ('segmented') model is feasible, but it would require smaller time-windows and a larger number of breakpoints, thus affecting model robustness.

Temporal autocorrelation, caused by non-independence of measuring units, confounding factors not included in the model or a combination of both, may result in biased estimates of parameters and their standard errors. To assess its effect on fitted models, we calculated the standardized residuals and used them to create autocorrelograms (i.e. autocorrelation plots relating ACF –the autocorrelation factor– against lag) up to a maximum lag of 20 days, using rstandard and acf functions, respectively, in R 3.6.3 (R Core Team, 2020) . Whenever significant autocorrelation was detected at certain lag values, we corrected its effect on model parameters and significance levels by modelling the autocorrelation in the response – i.e., by refitting a model incorporating the residuals into the linear predictor, for the specific lag detected. If significant autocorrelation was detected at more than one lag (two or, exceptionally, three), we refitted all possible models with one, two or three lags, and chose the most parsimonious one for which no residual autocorrelation and/or no improvement in model fit was obtained.

3.**Results**

The segmented models fitted successfully all regional data series (Figure 1). The use of segmented regression reduced greatly the level of temporal autocorrelation detected in the residuals (as compared to the linear model without breaking points), indicating that the successive changes in infection dynamics were the main source of such autocorrelation. Albeit much smaller, significant autocorrelation was still detected in 13 out of 16 regions, and required the incorporation of residuals at one (7 models), two (4 models) or three (one model) lag times. A lag=2 was the most frequent (9 models, including all those with several lags), while only three models required a lag larger than two days.

The number of breakpoints ranged from only two (in Castilla-León and the Basque Country) to a maximum of eight (in Asturias). Note that, hereafter, references to the

association between breakpoints and management measures will already apply the expected 6-day delay between infection and symptom onset (as indicated in Figure 1's upper X-axis arrows).

In most regions (14 out of 16), significant decreases in Rt preceded the onset of the nationwide lockdown (albeit with a considerable delay for Balearic Islands; Figure 1, Table S1). Indeed, in Madrid, Catalonia and Castilla-León, the drop in Rt that started before the national lockdown simply continued at the same rate after it. In contrast, in the Basque Country and La Rioja Rt kept increasing until 26-27 March and showed a turning point corresponding to infections taking place five days after the enforcement of the nationwide lockdown. Moreover, in at least one region (Aragón), the decrease in Rt previous to the nationwide lockdown was interrupted by a period of significant increase in Rt values that coincided with its commencement; while in eight more regions (Castilla-La Mancha, Andalusia, Valencia, Galicia, Navarra, Extremadura, Cantabria and Murcia), it coincided with a breakpoint after which Rt decreased more slowly – i.e., it showed significant, albeit smaller slopes (see Figure 1).

The enforcement of the nationwide lockdown is associated to the strongest and most widespread decrease in Rt in the whole dataset. In all regions, the lockdown resulted in a swift (and highly significant) decrease in Rt until reaching values <1 (indicating the switch from the spread to the control phases of infection dynamics) and stabilizing there. In contrast, the subsequent enforcement of the strengthened lockdown (cessation of all non-essential economic activity) seemed to have limited to no impact on the containment of the epidemic: it coincided with no additional decreases in Rt, and was associated instead to switches to significant, positive slopes (Rt increases) in at least seven regions (Castilla-León, Andalusia, Galicia, Extremadura, Cantabria, Balearic Islands and Murcia). In general, the period between the onset and the end of the strengthened lockdown was characterized by low Rt values (below or slightly above 1) and either flat or fluctuating trends.

The end of the strengthened lockdown was closely associated with major changes in the infection trends, with significant, long term increases in Rt in at least four regions (Castilla-León, Castilla-La Mancha, Navarra and Balearic Islands); and significant, shorter-term increases in two more (Extremadura and Asturias).

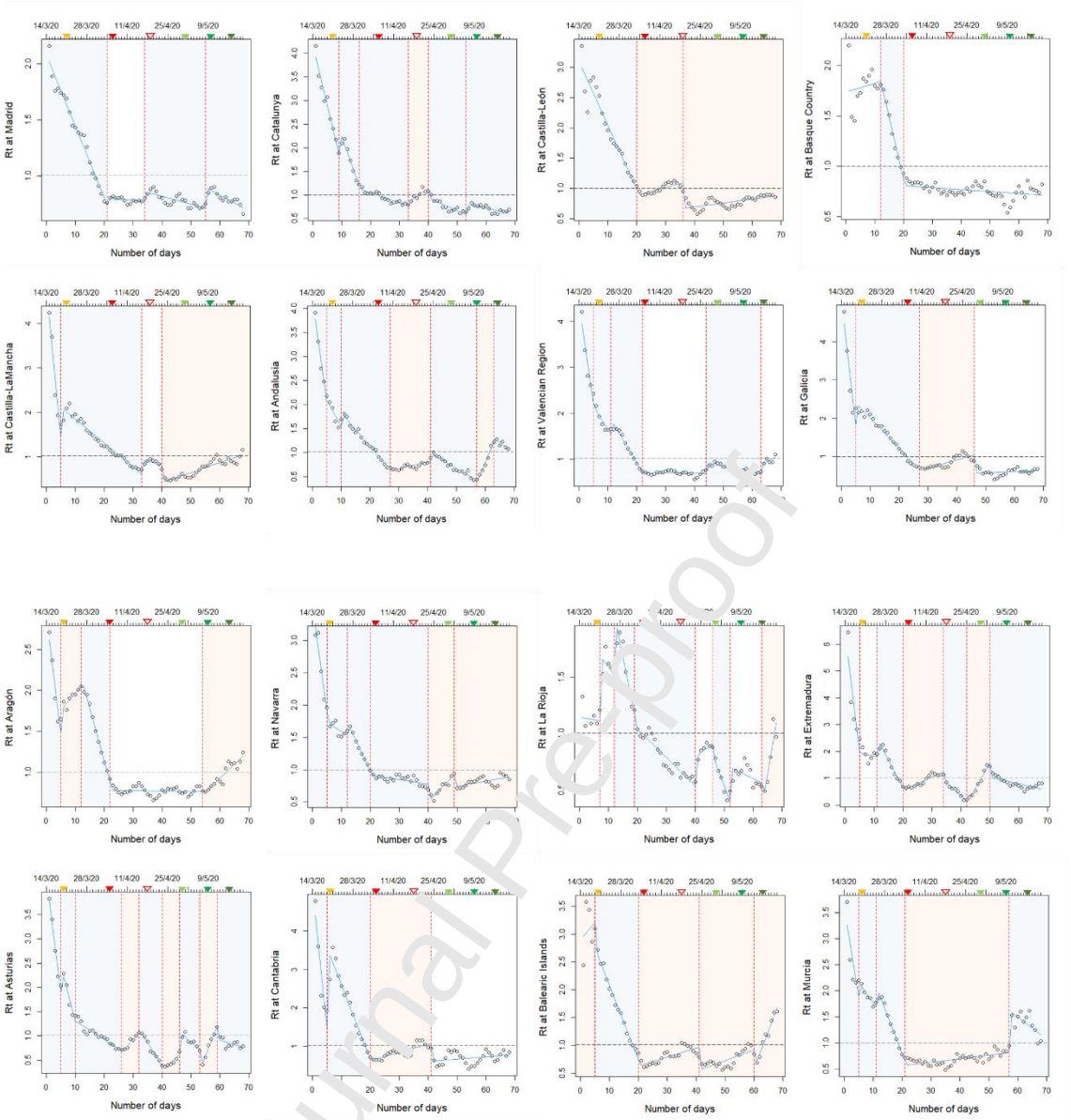

Figure 1. Results of segmented regressions on the effective reproduction number (Rt) of the COVID19 pandemic in the different autonomous regions of Spain. In the upper X axes (dates), colored triangles indicate the estimated detection times of infections taking place at the onset of key policy measures: orange = nationwide lockdown (15 March); filled red = strengthened lockdown (31 March); empty red = end of the strengthened lockdown (13 April); light and medium green = relaxation of lockdown for children (26 March) and elderly/adults (4 May), respectively; dark green = phase 1 of de-escalation program (variable among regions). Red broken lines indicate breakpoints. Blue and red areas respectively indicate segments with significant increases and decreases in Rt.

Finally, the de-escalation coincided with sudden and sustained increases in Rt in seven regions (Andalusia, Valencia, Aragón, La Rioja, Asturias and Balearic Islands), and with the maintenance of the increasing trends initiated after the end of the strengthened lockdown in three more (Castilla-León, Castilla-La Mancha and Navarra).

Strikingly, the likelihood of switching to an increase in Rt values was higher in regions that were hit less hard by the pandemic. There was a significant, negative relationship between the incidence of the pandemic (rank based on the number of cases per capita in each region, at the onset of each given period) and the occurrence of Rt increases during the strengthened lockdown (logistic regression with probit link: χ^2=7·29, df=1, P<0·007; Figure 2), but not after ending the strengthened lockdown or in the relaxation+de-escalation period (χ^2=0·87, df=1, P>0·35 and χ^2=0·37, df=1, P>0·54, respectively). For the strengthened lockdown, a similar relationship was found when regressing the duration of Rt increases (number of days per period) on the number of cases per capita in each region (y = 8.982 – 5.167 * log(x), χ^2=6·44, df=1, P<0·011).

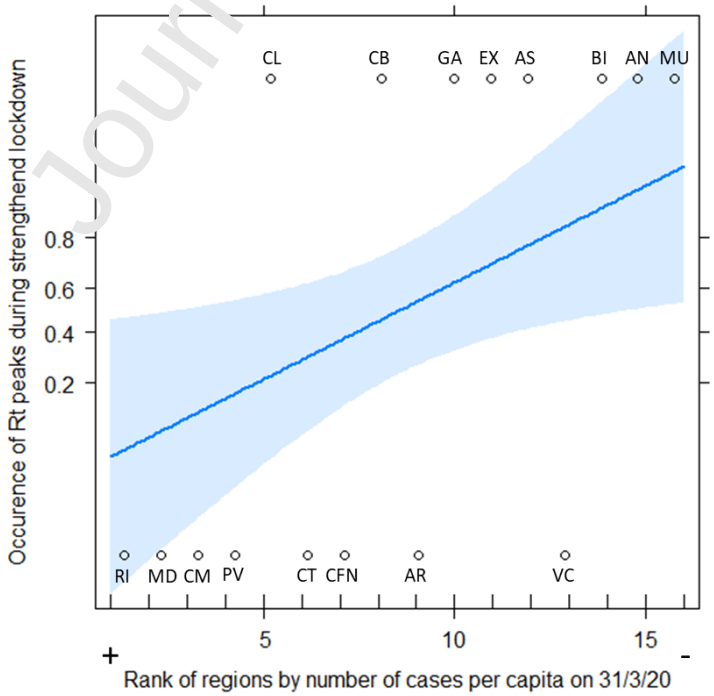

Figure 2. Relationship between the occurrence of increases in effective reproduction number (Rt) during the strengthened lockdown and the rank of incidence (from higher to lower number of cases per capita) in each Spanish region.

4.Discussion

Our results show that the different public health measures taken by the Spanish national and regional governments resulted in significant decelerations of COVID-19 progress, albeit with some regional differences. First, we detect an early deceleration in the spread of the pandemic in most regions, probably associated to personal hygiene and social distancing recommendations that preceded the enforcement of the nationwide lockdown (as discussed in Santamaría & Hortal, 2020). After that, the nationwide lockdown marks a clear turning point in the effective reproduction number: the strong decrease in Rt detected in all regions either commences or continues after such enforcement (Tobías, 2020). However, in nine regions the decrease in Rt that preceded the nationwide lockdown was interrupted by increases in Rt values at its onset (most notably Aragón, Castilla-La Mancha, Navarra and Extremadura). It is likely that these increments are associated to the increases in inter-regional mobility from the most affected regions (Madrid, Catalonia, Basque Country and La Rioja; Mazzoli et al., 2020), triggered by local lockdown measures (such as the closure of schools and universities in Madrid and parts of the Basque Country, in March 11) and by the anticipated announcement of the national lockdown (two days before its implementation). These uncoordinated regional reactions unwittingly incentivized the migration of students and wealthy citizens to family homes and second residences outside of the big cities, producing a "centrifuge multi-seeding" response that has been also observed in other countries, such as France and the US (Onishi & Méheut, 2020; Hoffower, 2020).

In contrast with this strong effect, the ulterior strengthening of the lockdown imposed on March 31st was not associated to further Rt decreases in any region. Instead, it showed counter-intuitive increases of transmission rate in several regions – with the four clearest examples involving coastal regions: Cantabria, Andalusia, Galicia and Balearic Islands. These responses may be the result of a combination of two factors. First, the relaxation and tiredness following several weeks of demanding lockdown in regions with a lower perception of risk. As our results show, these increases took place predominantly in the communities with lower COVID-19 incidence. Indeed, weekends showed a smaller reduction than weekdays in mobility during the lockdown phases (Pérez Arnal et al., 2020), evidencing that a small part of the Spanish population did continue moving outside their first residences (to second residences or for recreation) on a weekly basis – thereby facilitating the occurrence of new local outbreaks. Second, the leisure movements associated to the Easter holidays (from 4 to 13 April), which took place primarily in regions that represent major tourist destinations. Although the legal restrictions in force maintained overall mobility outside of the first residence below 10% of the baseline during the holidays period, analyses of mobile phone location data (INE, 2020) showed significant movements to coastal locations, both within and between regions. This is best exemplified by two regions: Balearic Islands and Murcia, which had the lowest number of cases within the dataset, but showed a concatenation of increases in Rt from the beginning of the strengthened lockdown, throughout its cessation, during the relaxation and the de-escalation periods, until the end of the time series analyzed.

The strengthened lockdown may have been instrumental, however, in maintaining the preventive tension and halting the recurrent spikes in Rt values – since its cessation was closely associated to long term increases in Rt in at least four regions (Castilla-León, Castilla-La Mancha, Navarra and Balearic Islands) and shorter-term increases in two more (Extremadura and Asturias). As before, these changes may be related to increased inter-regional mobility –

which, until then, was only authorized for transportation of essential goods and specialized personnel.

Importantly, the onset of the relaxation and de-escalation steps included in the time series seemingly caused sudden and sustained Rt increases in seven regions, and prolonged the increasing trends initiated after the cessation of the strengthened lockdown in three other ones. These responses are not significantly associated to the incidence of the pandemic until that date, and contrast with the generalized decreasing trends in the use of Facebook and Google (associated with increased mobility) after the lockdown (Pérez Arnal et al., 2020). Rather, they seem to reflect a variability of causes across the different regions. For example, in two peripheral regions (Andalusia and Galicia), Rt increased during the strengthened lockdown and decreased after it ended. This may be associated to the displacement of workers, first coming from and then returning to industries placed at larger cities, such as Madrid (see Mazzoli et al. 2020; INE, 2020).

Data on Google and Facebook shows small differences between regions (Pérez Arnal et al., 2020), but does not allow to characterize the origin of these outbreaks. Given the high basal level of community transmission in most of Spain and its surrounding countries, these increases could be easily triggered by single contagion events at social gatherings. For example, in the last week of May, four holiday parties of around 20, 80, 15 and 30 attendants resulted in outbreaks at Lleida (Catalonia), the autonomous city of Ceuta, Badajoz (Extremadura) and Córdoba (Andalusia). The last example involved an infected Belgian resident who travel internationally to attend the party, despite all the restrictions in place. These events indicate that further research on mobility trends based on data from personal contact tracing by dedicated healthcare professionals (Hellewell et al., 2020; Salathé et al., 2020; Keeling et al., 2020) and mobile apps (Drew et al., 2020; Urbaczewski & Lee, 2020) is needed to understand the origin of the COVID-19 outbreaks during and after the de-escalation.

The results of such research will help elucidate the causes of the contrasting responses of the different Spanish regions detected in our analyses.

In summary, the swift decrease in Rt associated to the national lockdown in all regions, was followed by: (i) moderate increases in Rt during the strengthened lockdown in c. half of the regions; and (ii) stronger upward spikes during the early relaxation and de-confinement phases. These increases brought Rt back from values well below zero to values above such threshold, and thus represent a tangible risk of entering a second infection wave. These circumstances seem most inadequate to introduce the changes in the monitoring and reporting procedures, which caused the discontinuation of the official data, which is now composed of two different series (see section 2.1). A positive lesson may however be drawn from the early (pre-lockdown) decrease of Rt, caused primarily by voluntary hygiene and social distancing measures (Santamaría & Hortal, 2020). While economic pressures may have pressured the authorities into committing to an early de-escalation, responsible citizen behavior and a decided investment in contact tracing by the competent regional authorities could contribute significantly to contain the second wave of COVID-19 growth that has been already setting up throughout Spain since early August 2020.

Author contributions

Luis Santamaría: conceptualization, methodology, data gathering and curation, formal analysis, writing – all phases, visualization. **Joaquín Hortal:** conceptualization, methodology, writing – all phases, visualization.

Declaration of competing interest

We declare no competing interests. This research received no specific grant from any funding agency, commercial or not-for-profit sectors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Spanish Research Council (CSIC). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Not required.

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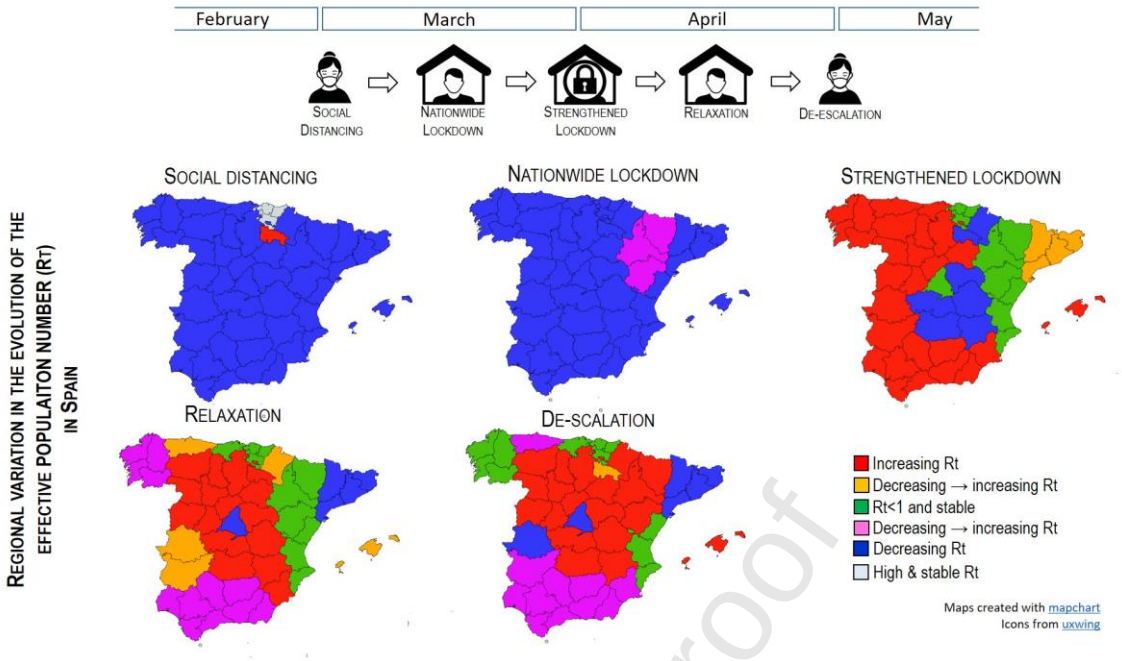
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

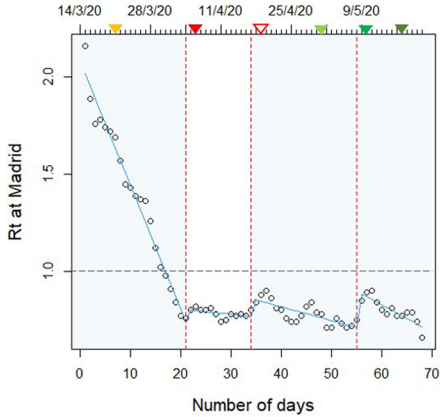
Author contributions

Luis Santamaría: conceptualization, methodology, data gathering and curation, formal analysis, writing – all phases, visualization. **Joaquín Hortal:** conceptualization, methodology, writing – all phases, visualization.



Highlights:

- Public health and movement restriction measures can limit the spread of infectious diseases in highly-populated regions.
- We associate governmental containment measures with the dynamics of COVID-19 transmission in Spain.
- The national lockdown successfully decreased Rt in all regions, but the effectiveness of the strengthened lockdown varied considerably among regions.
- Increases in transmission are associated with higher mobility within and between regions.
- Enhanced contact tracing is needed to prevent disease transmission without the need to recourse to new lockdowns.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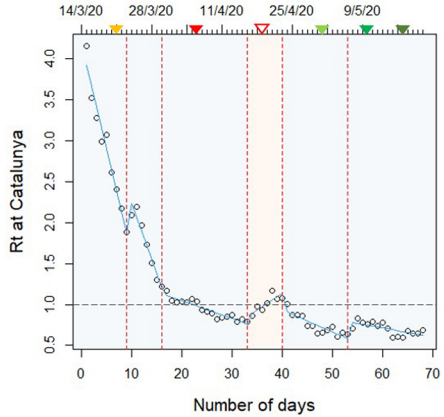
11/4/20
25/4/20
9/5/20
Rt at Madrid
Number of days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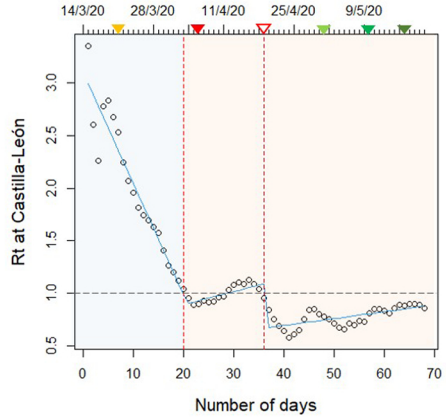
9/5/20
Rt at Catalunya
Number of days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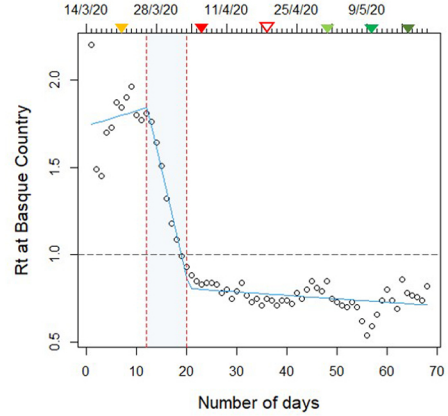
9/5/20
Rt at Castilla-León
Number of days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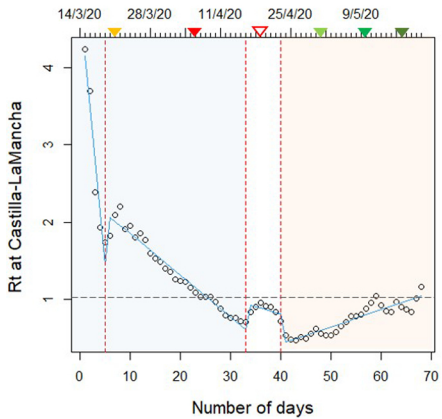
9/5/20
Rt at Basque Country
Number of days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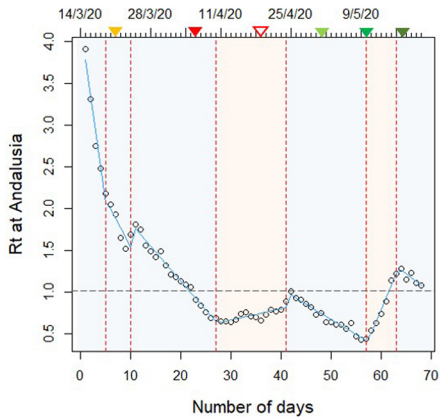
Rt at Castilla-LaMancha
Number of days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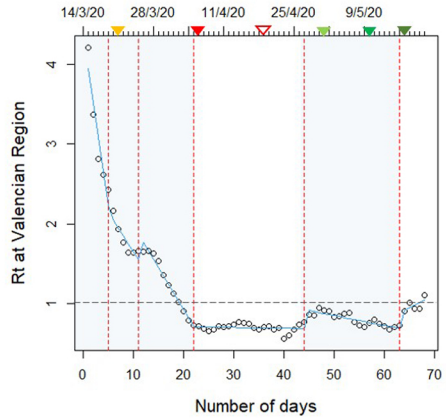
Rt at Andalusia
Number of days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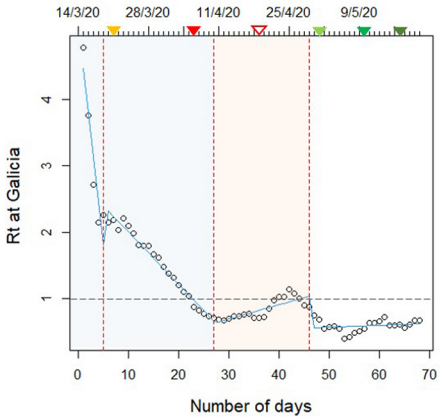
Rt at Valencian Region
Number of days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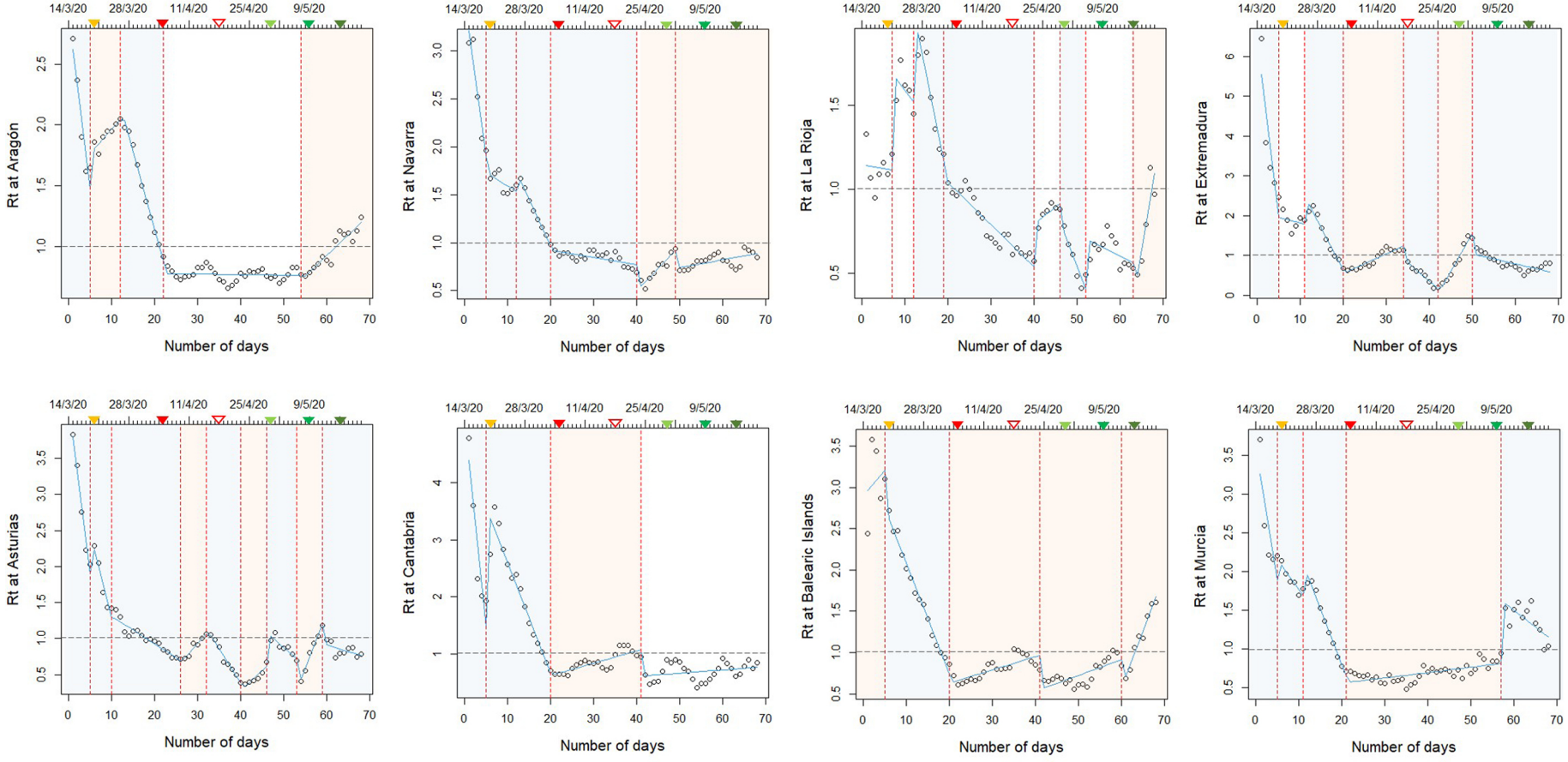
Rt at Galicia
Number of days

Figure 1r1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28/3/20
11/4/20
25/4/20
9/5/20
Rt at Aragón
Rt at Navarra
Rt at La Rioja
Rt at Extremadura
Rt at Asturias
Rt at Cantabria
Rt at Balearic Islands
Rt at Murcia
Number of days

Figure 1r2

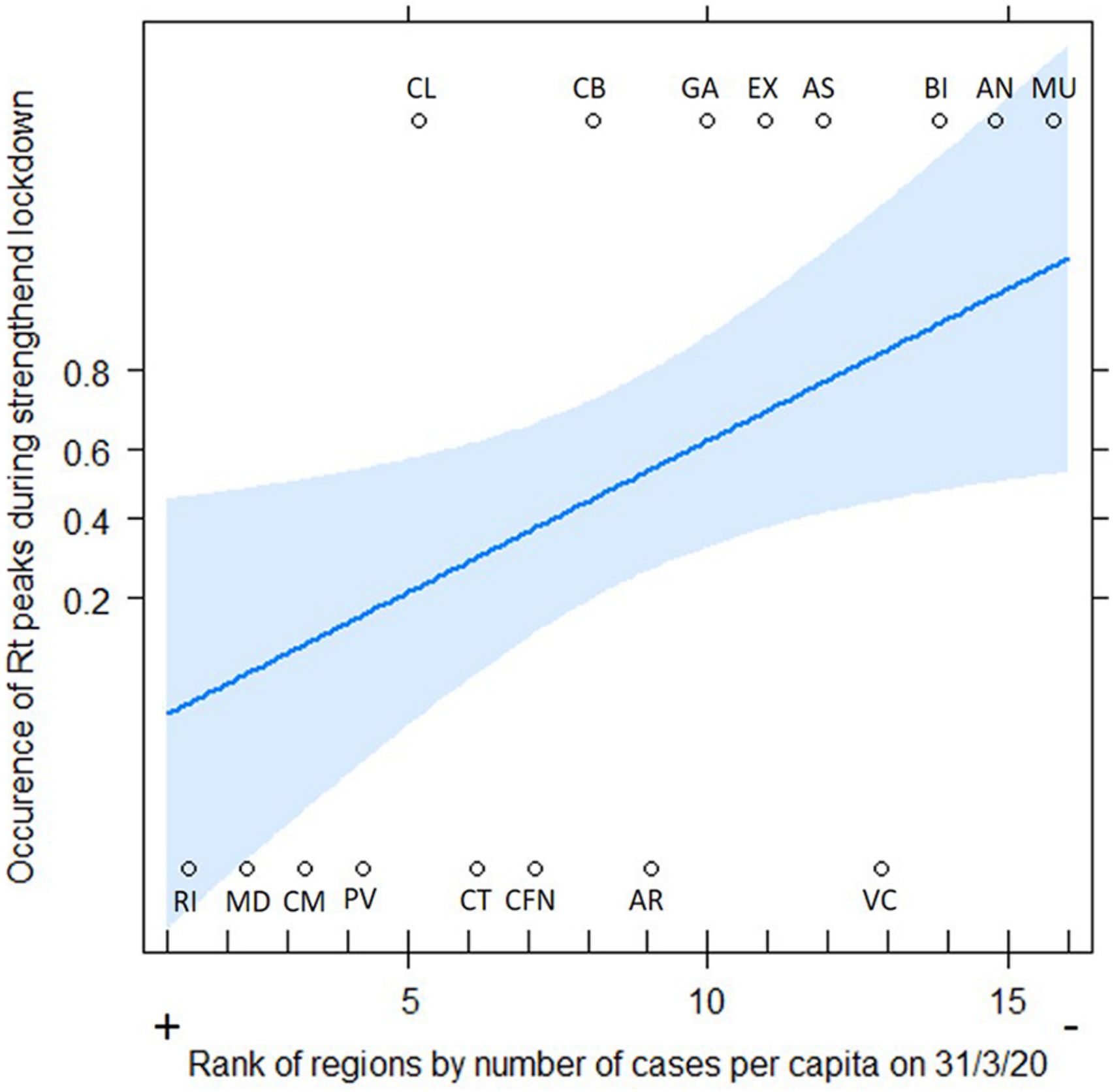
Occurence of Rt peaks during strengthend lockdown
0.8
0.6
0.4
0.2
CL
CB
GA
EX
AS
BI
AN
MU
RI
MD
CM
PV
CT
CFN
AR
VC
5
10
15
+
-
Rank of regions by number of cases per capita on 31/3/20

Figure 2